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Hyperfibrinolysis

Fibrinolysis is responsible for fibrin breakdown. Hyperfibrinolysis occurs when fibrinolytic activity is potentially greater than fibrin formation such that clot integrity is threatened. The central event of fibrinolysis is the generation of plasmin which cleaves fibrin and fibrinogen with the release of fibrin and fibrinogen degradation products. Free plasmin is rapidly inhibited by its inhibitor, α-2-antiplasmin. Fibrinolytic activity is initiated by the plasminogen activators, tissue plasminogen activator (t-PA) and urokinase (u-PA) which convert plasminogen to the active serine protease plasmin. t-PA is released by endothelial cells, has a short half life of three to five minutes and is regulated by specific inhibitors, plasminogen activator inhibitors (PAI) types 1 and 2. PAI-1 is the main systemic inhibitor and is produced by several cell types including endothelial cells, smooth muscle cells, fibroblasts, and hepatocytes; PAI-2 is found in the placenta.[1] Platelets are the source of 90% of the circulating PAI-1 antigen, which is released at the site of a forming thrombus. Hyperfibrinolysis occurs when the balance of fibrinolytic activators to their inhibitors is disturbed.[2]

The consequences of hyperfibrinolysis affect other aspects of haemostasis. Plasmin may reduce platelet adhesion and aggregation by degradation of receptor glycoprotein 1b and platelet fibrinogen receptor glycoprotein IIb/IIIa.[3] The consumption of clotting factors due to the direct effect of plasmin and the formation of fibrinogen degradation which inhibit fibrin polymerisation result in poor fibrin generation.

Fibrinolytic activation has been separated into primary and secondary fibrinolysis: primary fibrinolysis represents increased fibrinolytic activity independent of other factors, whereas secondary fibrinolysis is a consequence of activation of coagulation and thus thrombin generation which stimulates the endothelium to produce increased amounts of t-PA.

Chronic liver disease is a common cause of hyperfibrinolysis, and is characterised by both primary and secondary hyperfibrinolytic changes. There is reduced clearance of t-PA, and reduced concentrations of α-2-antiplasmin due to diminished protein synthesis: both primary changes.[4] Secondary hyperfibrinolysis is due to intravascular coagulation. These changes are related to the severity of liver disease as is clearly shown by El-Bassiouni *et al* [5] in patients with hepatosplenic schistosomiasis. In cirrhotic patients ascites is frequently associated with hyperfibrinolysis; and in a multivariate analysis of risk factors for bleeding in over 100 cirrhotic patients, hyperfibrinolysis, as measured by high values of D-dimer and t-PA activity, was the only predictor of gastrointestinal bleeding, a major cause of morbidity and mortality in liver failure.[6] During orthotopic liver transplantation the precarious fibrinolytic state of chronic liver disease is exacerbated during the anhepatic phase of surgery; exceptionally high concentrations of t-PA are found when the donor liver is first perfused by the recipient's circulation.[7] This may relate to plasminogen activator release from perturbed donor liver endothelial cells caused by hypoxia and acidosis.[8]

Other surgical procedures induce hyperfibrinolytic changes, notably the use of cardiopulmonary bypass in cardiac surgery, characterised by increased t-PA concentrations during bypass: this is responsible in part for the perioperative bleeding diathesis seen in cardiac surgery patients.[9] Hyperfibrinolysis may be iatrogenic due to the use of fibrinolytic agents in removing thrombus after arterial or venous thromboembolism.

Measurement of fibrinolytic activity is difficult in the face of low fibrinogen concentrations. Increased levels of fibrin degradation product titres (usually D-dimers which are the degradation products from cross-linked fibrin) are used routinely as a quick marker of increased fibrinolytic activity. However, they are crude and in situations such as postoperative bleeding are not useful, for concentrations are increased postoperatively in all patients. In such situations it would be helpful to know the levels of plasminogen activators, but these assays are time consuming and expensive. The thromboelastograph is the most useful instrument used in the surgical setting to determine the fibrinolytic status of a patient. It is relatively simple, small, and inexpensive so that it can be used in theatre, without a pathology technician. Moreover, it has the advantage of giving a picture of all haemostatic parameters. It is criticised, however, for being crude and poorly reproducible: but often during surgical bleeding an approximate guide to the state of haemostasis is all that is required. The thromboelastograph is widely used during orthotopic liver transplantation[10] and its use is being extended to other surgical areas.

If clinical bleeding can be attributed to hyperfibrinolysis, then the use of an antifibrinolyic agent is appropriate. Aprotinin is a powerful antiplasmin agent that, when given continuously perioperatively, reduces bleeding during cardiac surgery[11] and is also used extensively during orthotopic liver transplantation.[8] In established bleeding it can be given at a dose of 500 000 KIU intravenously in an emergency. Tranexamic acid and epsilon aminocaproic acid (EACA) also have antiplasmin properties but are less efficacious than aprotinin.

Finally, hyperfibrinolysis is not always harmful; it can even be considered beneficial, notably in disseminated intravascular coagulation. In this situation the use of an antifibrinolytic agent is contraindicated as fibrinolytic activation prevents permanent end organ damage as a result of microvascular fibrin deposition.

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